Bayer HealthCare
Consumer Care Division

June 21, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

SUBJECT: **Citizen Petition for Phenylephrine Bitartrate**
Docket No. 76N-052N/CP18
Response to FDA Request for Additional Information

Bayer HealthCare LLC
Consumer Care Division
36 Columbia Road
P.O. Box 1910
Morristown, NJ 07962-1910

Phone: 973 254-5000

Please refer to our Citizen Petition dated March 20, 2002, submitted under Docket No. 76N-052N/CP18, to have phenylephrine bitartrate (PEB) included as a generally recognized as safe and effective (GRAS/E) oral nasal decongestant active ingredient in the Cough, Cold, Allergy, Bronchodilator and Anti-asthmatic Drug Products for Over-the-Counter Human Use Final Monograph.

Per FDA request enclosed please find a copy of the proposed monograph for PEB published in the May-June 2004 *USP-Pharmacopeial Forum*. PEB is targeted to be included in Supplement 1 to *USP 28-NF 23*.

According to the May-June 2004 *USP Pharmacopeial Forum*, the publication and comment schedule for Supplement 1 to *USP 28-NF 23* is as follows:

Comment Deadline:	October 15, 2004
Publication Date:	February 2005
Official Date:	April 2005

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Bayer hopes this additional information is helpful to the Agency in its ongoing review of this Citizen Petition. Please do not hesitate to contact me (973-408-8046) with any additional questions or comments.

Sincerely,
Bayer HealthCare LLC
Consumer Care Division

William R. Walsh
Senior Associate Director
Regulatory Affairs

Submitted in duplicate
Desk Copy to G. Rachanow

BRIEFING

Phenylephrine Bitartrate. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Chromatographic purity* are based on analyses performed with the Symmetry brand of L1 column. The typical retention times are about 2.0 for norphenylephrine, about 2.2 for (–)-phenylephrine, about 2.6 for phenylephrone, about 6.4 for 1-benzylphenylepherine, and about 6.9 for benzylphenylepherine HCl.

(PA1: C. Anthony) RTS—39860-1

Add the following:

■ **Phenylephrine Bitartrate**
$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.3

R-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol, hydrogentartrate.
(–)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogentartrate.
(–)-3 Hydroxy-α [(methylamino) methyl] benzenemethanol, hydrogentartrate.
1-*m*-Hydroxy-α-[(methylamino) methyl] benzylalcohol, hydrogentartrate [*17162-39-0*].

» Phenylephrine bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{13}NO_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Packaging and storage— Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩— *USP Phenylephrine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The alkaline of tartrate from the test for *Specific rotation* responds positively to the test for *Tartrate* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –53° and –57° for the prepared sample.

Test solution— Prepare a sample solution of about 24 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at 105° for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.

pH ⟨791⟩**:** between 3.0 and 4.0 in 10% w/v aqueous solution.

Loss on drying ⟨731⟩— Dry at 105° to a constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Chromatographic purity—

Buffer solution— Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8.

Solution A— Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (9:1).

Solution B— Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (9:1).

Diluent— Prepare a mixture of *Solution A* and *Solution B* (8:2).

System suitability solution— Dissolve accurately weighed quantities of USP Phenylephrine Hydrochloride RS, norphenylephrine hydrochloride, 1-benzylphenylepherine base, and benzylphenylepherine hydrochloride in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.06 mg per mL, 0.09 mg per mL, 0.07 mg per mL, and 0.05 mg per mL, respectively.

Test solution— Transfer 78 mg of phenylephrine bitartrate, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a 215-nm detector and a 5.5-cm × 4-mm column that contains packing L1. The column temperature and injector temperature are maintained at 45 ± 2°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	93	7	equilibration
0–10	93→30	7→70	linear gradient
10–18	30	70	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for norphenylephrine, about 1.0 for (–)-phenylephrine, about 1.2 for phenylephrone, about 2.9 for 1-benzylphenylepherine, and about 3.1 for benzylphenylepherine HCl.

The resolution, *R,* between norphenylephrine and (–)-phenylephrine is not less than 1.5. The tailing factor of (–)-phenylephrine is less than 1.8. The relative standard deviation for replicate injections is not more than 6%.

Procedure— Inject about 10 µL of the *Test solution* into the chromatograph, record the

chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Phenylephrine Bitartrate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.2% of any individual impurity is found, and not more than 0.5% of total impurities is found.

Assay— Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a 100-ml beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration and make the necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N $HClO_4$ is equivalent to 31.73 mg of $C_9H_{13}NO_2 \cdot C_4H_6O_6$. ■1S (*USP28*)

Auxiliary Information— *Staff Liaison* : Daniel K. Bempong, Ph.D., Scientist
Expert Committee : (PA2) Pharmaceutical Analysis 2
Pharmacopeial Forum : Volume No. 30(3) Page 923
Phone Number : 1-301-816-8143